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TITLE: A Randomized Phase 2 Trial of 177Lu Radiolabeled Anti-PSMA Monoclonal Antibody J591in Patients with High-Risk Castrate, Biochemically Relapsed Prostate Cancer

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14. ABSTRACT

Clinical trial has received WCMC IRB and CTSC approval with enrollment of initial 5 subjects at WCMC. An additional 18 subjects enrolled (15 treated) at participating sub-sites. Reports submitted to WCMC DSMB with recommendation to proceed with enrollment.

15. SUBJECT TERMS

Prostate cancer, PSA, PSMA, monoclonal antibody, radioimmunotherapy

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I. Introduction

Men with biochemically progressive (PSA only) prostate cancer have non-radiographically apparent micrometastases that may be targeted with radioimmunotherapy. Prostate specific membrane antigen (PSMA) is the single, most well-established, highly restricted prostate epithelial cell membrane antigen known and is expressed by virtually all prostate cancers. Investigators at WCMC have generated a high-affinity antibody (J591) against the external portion of PSMA that binds to viable PSMA-expressing cells and is internalized. Studies utilizing J591 radiolabeled with Lutetium-177 (^{177}Lu) have demonstrated safety, efficacy, and accurate, selective tumor targeting in the metastatic castration-resistant prostate cancer (CRPC) setting. The physical properties of ^{177}Lu are best suited for 1-3 mm tumors (those not seen on standard imaging modalities). The hypothesis is that the addition of ^{177}Lu-J591 to ketoconazole will improve time to radiographically apparent metastases in men with biochemically progressive non-metastatic CRPC.

In this multi-center, double-blind, randomized phase II trial involving men with relapsed prostate cancer and biochemical only (PSA) progression (no radiographic evidence of metastases) despite castration at high risk of early development of metastases. The primary endpoint will be to compare the percentage of men with metastases at 18 months receiving ketoconazole plus ^{177}Lu-J591 vs ketoconazole plus trace-labeled ^{111}In-J591 (i.e. placebo). Secondary endpoints include PSA response, toxicity, progression-free survival, overall survival, the ability of radiolabeled J591 to image otherwise non-radiographically apparent metastatic sites, the prognostic and predictive capability of circulating tumor cells, baseline adrenal androgen levels, and circulating markers of hemostatic activation, fibrinolysis, and angiogenesis. With a sample size of 127 (2:1 randomization), the study will have a ≥ 0.80 power with a pre-set alpha of 5% to determine an absolute difference in 18-month metastasis free survival. An interim analysis after 12 months of follow-up will be performed and reviewed by the external DSMB (necessitating increase in sample size by 10% to 140). Stopping limits will be imposed such that a significant observed difference in the metastasis-free proportion will be grounds for the consideration of early termination of the study using an adjusted significance level corresponding to the O'Brien-Fleming group sequential rule.

II. Body

Overview:

- 5 subjects have been enrolled and treated at Weill Cornell Medical College with two additional screen failures and at least 25 pre-screen failures.
- 10 subjects have been enrolled and treated to date at Indiana University with additional pre-screen and screen failures
- 4 subjects have been enrolled at University of Iowa with 3 treated (1 screen failed)
- 4 subjects have been enrolled with 2 treated to date at University of Southern California (2 screen failures) with at least 2 additional pre-screen failures.

SOW Task **1a**, **1b**: Additional sites are in various stages of regulatory approval:

IRB Approved and site activated:
- Weill Cornell Medical College (IRB Approved 09Jan2009)
- University of Iowa (IRB Approved 24Jun2010)
- Indiana University (IRB Approved 29Jun2010)
- University of Southern California (IRB Approved 10Jan2011)
- Emory University (IRB Approved 20Jul2011); site on hold with re-activation 09Sep2012
- Cedars-Sinai (IRB Approved 14Jun2012)
- University of Utah (IRB Approved 27Jun2012)

IRB Approval in progress:
- Georgetown University Hospital, Washington, DC – IRB approved; pending contract signatures
- University of Kansas – scientific and radiation safety committee approved; pending IRB approval
- University of Medicine and Dentistry, New Jersey – in scientific review
- UAB Comprehensive Cancer Center, Alabama – scientific and radiation safety committee approved; pending IRB approval and contract review
- MD Anderson Cancer Center Orlando – radiation safety approved; IRB review pending
- Jesse Brown, VA/University of Illinois at Chicago
- Vanguard Urology, Houston, TX – budget/contract approval in process; IRB review pending
-

Anticipated to initiate IRB start-up:
- University of Pittsburgh Medical Center
- Jesse Brown, VA/University of Illinois at Chicago
- Washington University

The study is currently being primarily offered via the CTSA and PCCTC groups (see "Problem Areas" below)

SOW Task **1a,b,c**: Amendments have been approved by ORP and WCMC IRB

Task **2a,b**: See above

Task **3a,b,c**: Safety lead-in phase completed, reported, reviewed by DSMB

Task **4a**: see above
Task **4b**: Weekly email communication with sites, phone/teleconferences when necessary; Overall study re-invigoration investigator meeting being scheduled for October 2012
Task **4c**: Ongoing IRB and FDA updates; last DSMB submission May 2012.

III. Key Research Accomplishments

- The protocol has been approved by the WCMC IRB and CTSC as well as ORP, 6 investigational sites activated as of September, 2012

- The study was presented as a poster presentation at the 2010 and 2011 annual scientific meeting of the American Society of Clinical Oncologists
- Manuscript detailing background and rationale for the study has been published
- Obtained assistance from a professional Clinical Research Organization (CRO) to assist with study start-up, source document verification, and recruitment.
- A subject recruitment advertisement has been sent to print and will be submitted for WCMC IRB review shortly.
- "Dear Doctor" referral letters have been drafted and sent to participating institutions

IV. Reportable Outcomes

Tagawa ST, Hahn NM, Vaena DA, Quinn DI, Kelly WK, Christos PJ, Osborne J, Vallabhajosula S, Nadeau K, Mileo G, Tyrell L, Saran A, Ecker C, Beltran H, Goldsmith SJ, Nanus DM. Radiolabeled anti-prostate specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) for nonmetastatic castration-resistant prostate cancer (CRPC): A randomized phase II trial. *J Clin Oncol* 29: 2011 (suppl; abstr TPS193)

Presentation: Poster presentation, 2011 ASCO Annual Meeting

Kosuri S, Akhtar NH, Smith MJ, Osborne J, Tagawa ST. Review of salvage therapy for biochemically recurrent prostate cancer: The role of imaging and rationale for systemic salvage targeted anti-prostate specific membrane antigen radioimmunotherapy. *Adv Urol* 2012, Article ID 921674, doi:10.1155/2012/921674

V. Conclusions

Biochemical relapse is common after local therapy for prostate cancer. Based on the physical properties of ^{177}Lu and the disease targeting ability of J591, ^{177}Lu-J591 is ideally suited to make a significant impact on this state of disease. The protocol has been approved and activated at the initial sites and progress continues at additional sites.

VI. References

None used

VII. Appendices

Attachment 1: Tagawa et al. abstract, J Clin Oncol 29: 2011 (suppl; Abstr TPS193)

Attachment 2: Poster presentation, ASCO 2011

Attachment 3: Kosuri et al manuscript, Adv Urol 2012

Attachment 4: Approval documents: (a) Most recent WCMC IRB approval document, (b) Most Recent DSMB Approval, and (c) Emory IRB approval (d) Cedars-Sinai IRB approval (e) Utah IRB approval

Attachment 5: "Dear Doctor" Referral Letter

ASCO American Society of Clinical Oncology
www.asco.org

Radiolabeled anti-prostate specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) for nonmetastatic castration-resistant prostate cancer (CRPC): A randomized phase II trial.

Sub-category:
Prostate Cancer

Category:
Genitourinary Cancer

Meeting:
2011 ASCO Annual Meeting

Session Type and Session Title:
Trials in Progress Poster Session, Trials in Progress Poster Session

Abstract No:
TPS193

Citation:
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Author(s):
S. T. Tagawa, N. M. Hahn, D. A. Vaena, D. I. Quinn, W. K. Kelly, P. J. Christos, J. Osborne, S. Vallabhajosula, K. Nadeau, G. Mileo, L. Tyrell, A. Saran, C. Ecker, H. Beltran, S. J. Goldsmith, D. M. Nanus; Weill Cornell Medical College, New York, NY; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; University of Iowa, Iowa City, IA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Thomas Jefferson University Hospital, Philadelphia, PA

Abstract Disclosures

Abstract:

Background: Biochemical recurrence without evidence of PC on standard CT/MRI and bone scans after local therapy is common. Salvage radiotherapy affords a cure to select patients (pts) with PSA relapse, but most progress because of micrometastatic PC outside of the radiation field. J591 is a monoclonal antibody that targets the extracellular domain of PSMA. A phase II trial of single-dose ^{177}Lu-J591 radioimmunotherapy (RIT) in pts with progressive, metastatic (met) CRPC demonstrated excellent targeting of met sites, efficacy, and acceptable toxicity [Tagawa et al, ASCO 2008]. RIT appears to have its greatest impact in the setting of minimal disease [Kaminski, NEJM 2005; Leonard, JCO2005; Press, JCO 2006] and the beta emission of ^{177}Lu is best suited for lesions 1-3 mm in diameter [O'Donoghue, J Nuc Med 1995] (i.e. micrometastatic disease). **Methods:** In this multicenter DOD-sponsored study, men with high-risk CRPC (PSA doubling time < 8 months and/or PSA > 20 [Smith, JCO 2005]) and no evidence of disease on CT/MRI and bone scans are randomized 2:1 to receive double-blinded ^{177}Lu-J951 vs ^{111}In-J591 (control) and undergo planar gamma camera imaging with SPECT following infusion. All pts receive ketoconazole plus hydrocortisone. The primary endpoint of the study is 18-month met-free survival. 140 pts will be treated to allow 80% power with a 2-sided alpha of 5% to detect a 25% absolute difference (50% vs 75% met-free) in radiographically apparent mets at 18 months (with interim analysis after 50% of pts have at least 12 months follow up). Secondary/exploratory endpoints include evaluation of radiolabeled J591 imaging to detect sites of mets not apparent on standard CT/MRI and bone scan, validation of adrenal androgen levels as biomarkers for ketoconazole [Ryan Clin Cancer Res 2007], analysis of circulating tumor cells captured via CellSearch methodology as well as PSMA-GEDI capture [Gleghorn, Lab Chip 2010] for PSMA expression and counts to predict the appearance of radiographic metastases, and exploration of hemostatic/fibrinolytic/angiogenic plasma biomarkers.

Associated Presentation(s):

1. Radiolabeled anti-prostate specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) for nonmetastatic castration-resistant prostate cancer (CRPC): A randomized phase II trial.

Meeting: 2011 ASCO Annual Meeting

Presenter: Scott T. Tagawa
Session: Trials in Progress Poster Session (Trials in Progress Poster Session)

Other Abstracts in this Sub-Category:

1. SYNERGY: A randomized phase III study comparing first-line docetaxel/prednisone to docetaxel/prednisone plus custirsen in metastatic castrate-resistant prostate cancer (mCRPC).

Meeting: 2011 ASCO Annual Meeting Abstract No: TPS180 First Author: K. N. Chi
Category: Genitourinary Cancer - Prostate Cancer

2. A randomized, double-blind, phase III trial comparing ipilimumab versus placebo following radiotherapy (RT) in patients (pts) with castration-resistant prostate cancer (CRPC) who have received prior treatment with docetaxel (D).

Meeting: 2011 ASCO Annual Meeting Abstract No: TPS181 First Author: C. G. Drake
Category: Genitourinary Cancer - Prostate Cancer

3. Randomized, double-blind, phase III trial to compare the efficacy of ipilimumab (Ipi) versus placebo in asymptomatic or minimally symptomatic patients (pts) with metastatic chemotherapy-naïve castration-resistant prostate cancer (CRPC).

Meeting: 2011 ASCO Annual Meeting Abstract No: TPS182 First Author: T. M. Beer
Category: Genitourinary Cancer - Prostate Cancer

More...

Abstracts by S. T. Tagawa:

1. Clinical outcome of single agent volasertib (BI 6727) as second-line treatment of patients (pts) with advanced or metastatic urothelial cancer (UC).

Meeting: 2011 ASCO Annual Meeting Abstract No: 4567 First Author: W. M. Stadler
Category: Genitourinary Cancer - Other GU Cancer

2. Final phase II results of NCI 6981: A phase I/II study of sorafenib (S) plus gemcitabine (GEM) and capecitabine (CAP) for advanced renal cell carcinoma (RCC).

Meeting: 2011 ASCO Annual Meeting Abstract No: e15165 First Author: S. T. Tagawa
Category: Genitourinary Cancer - Kidney Cancer

3. Molecular characterization of neuroendocrine prostate cancer (NEPC) and identification of new drug targets.

Meeting: 2011 ASCO Annual Meeting Abstract No: 4536 First Author: H. Beltran
Category: Genitourinary Cancer - Prostate Cancer

More...

Presentations by S. T. Tagawa:

1. Radiolabeled anti-prostate specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) for nonmetastatic castration-resistant prostate cancer (CRPC): A randomized phase II trial.

Meeting: 2011 ASCO Annual Meeting
Presenter: Scott T. Tagawa, MD, MS
Session: Trials in Progress Poster Session (Trials in Progress Poster Session)

2. A randomized phase II trial of ^{177}lu radiolabeled monoclonal antibody J591 (^{177}Lu-J591) and ketoconazole in patients (pts) with high-risk castrate biochemically relapsed prostate cancer (PC) after local therapy.

Meeting: 2010 ASCO Annual Meeting

Presenter: Scott T. Tagawa
Session: Trials in Progress Poster Session (Trials in Progress Poster Session)

3. Phase I trial of fractionated-dose ^{177}lutetium radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) in patients (pts) with metastatic castration-resistant prostate cancer (metCRPC).

Meeting: 2010 ASCO Annual Meeting
Presenter: Scott T. Tagawa
Session: Genitourinary Cancer (General Poster Session)

More...

▸ ***Educational Book Manuscripts by S. T. Tagawa*:**

No items found.

RADIOLABELED ANTI-PROSTATE SPECIFIC MEMBRANE ANTIGEN (PSMA) MONOCLONAL ANTIBODY J591 (^{177}Lu-J591) FOR NON-METASTATIC CASTRATION-RESISTANT PROSTAT CANCER (CRPC): A RANDOMIZED PHASE II TRIAL

Scott T. Tagawa, Noah Hahn, Daniel Vaena, David Quinn, Mark Stein, Joseph Osborne, Paul J. Christos,
Shankar Vallabhajosula, Gina Mileo, Koty Nadeau, Lauren Tyrell, Ankeeta Saran, Himisha Beltran, Stanley J. Goldsmith, David M. Nanus
Weill Cornell Medical College, Indiana University, University of Iowa, University of Southern California, University of Medicine and Dentistry New Jersey

BACKGROUND

Radiolabeled J591

- J591 is a deimmunized anti-PSMA monoclonal antibody that binds to the extracellular domain of viable PSMA+ cells with rapid internalization
  Liu et al, Cancer Res 1997; Liu et al. Cancer Res 1998
- Phase I trials of radiolabeled J591 demonstrated safety, sensitive and specific tumor targeting, and preliminary evidence of activity
  Milowsky et al, JCO 2004, Bander et al, JCO 2005
- The MTD of ^{177}Lu-J591 was 70 mCi/m^2, with reversible myelosuppression

Phase II single-dose ^{177}Lu-J591 Radioimmunotherapy (RIT) for metCRPC

- Two successive cohorts of pts with progressive metCRPC received one dose of ^{177}Lu -J591: Cohort 1 (65mCi/m^2), 15 pts; Cohort 2: (70mCi/m^2, phase I MTD), 17 pts. The 1° endpoint was PSA and/or measurable disease response with 2° endpoint of toxicity. A ^{177}Lu-J591 imaging study was performed to confirm tumor targeting.
- Median age was 71 (range 51-88), median baseline PSA 81.6 (3.3 – 2184.6). 3 with ECOG PS 0, 27 PS 1, 2 PS 2; 97% had bone mets, 25% extra-osseous visceral mets (2 liver, 5 lung, 1 adrenal). The majority (18 pts, 56%) progressed on at least docetaxel.
- Overall, 3 (10%) experienced ≥ 50% PSA decline and 10 (31%) experienced ≥30% PSA decline. Those with PSA decline lived longer (p=0.01). Targeting of known sites of PC metastases was seen in 30 of 32 (94%) pts [Fig 1]. More pts treated at the phase I MTD (70 mCi/m^2) experienced PSA declines (71%) than those treated with 65mCi/m^2 (46%), p=0.06 [Fig 2].
- 9 pts received 1-4 platelet transfusions (median 2); no significant hemorrhagic complications occurred. Of 32 evaluable pts, 27 had return to normal platelet counts and 4 recovered to near-normal. 27% experienced transient Gr 4 neutropenia without fevers No serious attributable non-heme toxicity occurred.

Current/Future aims in metastatic CRPC

To develop biomarkers to optimally select pts (imaging may predict response, exploration of PSMA expression in CTC's), improve therapeutic profile with dose fractionation [Tagawa et al, ASCO 2010], and combine with chemo, utilizing improved tolerability of fractionated dose RIT + the radiosensitizing and debulking properties of docetaxel [Beltran et al; ASCO 2010].

The optimal setting for anti-PSMA RIT, especially based upon the physical properties of ^{177}Lu, may be micro-metastatic disease.

Supported by:
Department of Defense PC081664 (W81XWH-09-1-0596)
Prostate Cancer Foundation
NIH 1-KL2-RR024997-01; PTBF5405; ULI RR024996 (WCMC CTSC)

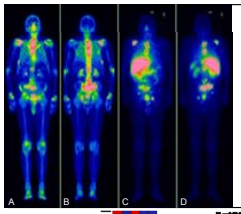


Figure 1

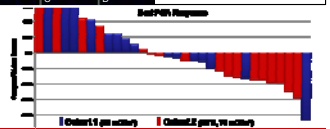
Left: ^{99m}Tc-MDP bone scan
Ant (A) and post (B) images of pre-treatment bony metastases

Right: ^{177}Lu-J591 scan
Ant (C) and post (D) total body images obtained via dual head gamma camera of sites of uptake 7 days after ^{177}Lu-J591 administration

(NOTE: J591 is cpartially leared via liver resulting in non-specific uptake)

Figure 2

Waterfall Plot of best PSA response



β Emitting Radionuclides: Rationale for ^{177}Lu-J591

		^{131}I	^{90}Y	^{177}Lu
Physical Half Life (days)		8.05	2.67	6.7
Beta Particles (mEv)	Maximum	0.61	2.280	0.497
	Average	0.20	0.935	0.149
Range in Tissue (mm)	Maximum	2.4	12.0	2.20
	Average	0.4	2.7	0.25
Gamma Emission (mEv)		0.364 (81%)	none	0.113 -0.208 (7-11%)

^{177}Lutetium: [O'Donoghue et al, J Nuc Med 2005]

- Low energy particle with short range
- Allow higher doses with less marrow toxicity
- Gamma emission allows imaging
- May be suboptimal for bulky tumors
  (i.e. suboptimal for disease state tested to date: metastatic CRPC)
- Physical properties more optimal for curability in small tumors (1-3 mm)

Radiolabeled (RL) J591 Efficacy

Over a decade of clinical experience
[Akhtar et al, ASCO GU 2011: 3 Ph I, 1 Ph 2 trials in 137 pts]

PSA declines: Majority (54%) with PSA declines

- More PSA declines at MTD doses (p<0.001 for ≥ 30% decline, p=0.05 for any)

Objective Radiographic Responses: (36.4% had measurable disease)

- More radiographic responses with ^{90}Y-J591 than ^{177}Lu-J591 (p=0.04)
- All pts with radiographic response also had significant PSA declines

CTC Counts: 84% became or remained favorable after RL-J591(n=19)

Survival: Overall Survival 16.6 mo [95% CI 13.4, 19.7]

- PSA decline associated with survival (22.1 vs 12.1 mo, p=0.001)

Salvage Anti-PSMA Radioimmunotherapy

- Biochemical only relapse is common, affecting approximately 50,000 new men per year in the U.S. alone
- PC is radiosensitive; salvage radiotherapy is an effective salvage therapy for selected pts, but most eventually suffer distant relapse/progression because of micrometastatic disease outside of the RT field [Ward J Urol 2004; Freedland J Urol 2007; Pazona J Urol 2005; Buskirk J Urol 2006; Stephenson JAMA 2004, JCO 2007]

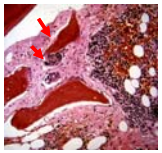


Figure 3

Sites of prostate cancer metastases (arrows) in bone marrow. These tumor deposits are too small to be detected on standard imaging and are not amenable to standard salvage therapy (external beam RT, surgery, cryotherapy, etc.)

- Radioimmunotherapy may have greatest effect in setting of minimal disease [Kaminski Blood 2002, JCO 2005, NEJM 2005; Press Blood 2003, JCO 2006; Leonard JCO 2005]
- Nearly all prostate cancer cells express PSMA [Israeli Cancer Res 1994; Silver Clin Cancer Res 1997; Bostwick Cancer 1998; Wright Urol Oncol 1995; Wright Urology 1996]
- J591 targets known sites of disease with efficacy in the advanced setting
- ^{177}Lu is optimal for 1-3 mm lesions, i.e. micrometastatic (small volume) disease not apparent on standard scans [O'Donoghue et al, J Nuc Med 2005]
- "Targeted radiotherapy" with ^{177}Lu-J591 may be able to eliminate sites of micrometastatic disease in the biochemically relapsed setting

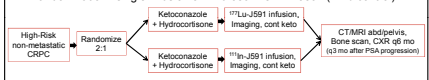
RANDOMIZED Ph II: Lu-J591 in NONMETASTATIC CRPC

ENTRY CRITERIA (summary)

- Biochemical relapse after primary local therapy
- High risk castrate-resistant PSA progression
  - rising PSA despite medical/surgical castration and testosterone < 50 ng/mL
  - absolute PSA > 20 and/or PSA DT < 8 mo
  [Smith et al, J Clin Oncol 2005]
- CT/MRI and bone scan without evidence of metastatic disease
- Intact hematologic and organ function
- ECOG Performance Status ≤ 2

TREATMENT

- All pts: ketoconazole 400 mg TID + hydrocortisone 20 AM, 10 PM
- 2:1 randomization: single infusion of ^{177}Lu-J591 vs ^{111}In-J591 (mAb control)



- 1° endpoint: metastasis-free survival at 18 months
  Based upon entry criteria, 50% expected to have mets at 18 months. With a sample size of 127 (2:1 randomization), ≥ 0.80 power with alpha of 5% to determine difference in 18-month metastasis free survival (75% vs 50%). Interim analysis after 50% of 18-month MFS events required for final analysis with futility analysis performed (increasing sample size to 140)
- 2° endpoints: ability of radiolabeled J591 to image micrometastatic disease, circulating tumor cell enumeration and PSMA expression, PFS, adrenal hormone levels, markers of hemostatic activation, fibrinolysis, angiogenesis

SUMMARY

Based upon the recurrence pattern of prostate cancer, its known radiosensitivity, J591's known ability to target sites of metastatic disease, and the physical properties of ^{177}Lu, anti-PSMA-based salvage RIT has the possibility of significantly impacting the natural course of relapsed prostate cancer

STATUS:

- The study is open at 4 centers and the initial subjects are accruing
- The study will open at additional sites throughout the United States, including sites in the CTSA consortium and Prostate Cancer Clinical Trials Consortium

Clinicaltrials.gov NCT00859781

Hindawi Publishing Corporation
Advances in Urology
Volume 2012, Article ID 921674, 8 pages
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Review Article

Review of Salvage Therapy for Biochemically Recurrent Prostate Cancer: The Role of Imaging and Rationale for Systemic Salvage Targeted Anti-Prostate-Specific Membrane Antigen Radioimmunotherapy

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Despite local therapy with curative intent, approximately 30% of men suffer from biochemical relapse. Though some of these PSA relapses are not life threatening, many men eventually progress to metastatic disease and die of prostate cancer. Local therapy is an option for some men, but many have progression of disease following local salvage attempts. One significant issue in this setting is the lack of reliable imaging biomarkers to guide the use of local salvage therapy, as the likely reason for a low cure rate is the presence of undetected micrometastatic disease outside of the prostate/prostate bed. Androgen deprivation therapy is a cornerstone of therapy in the salvage setting. While subsets may benefit in terms of delay in time to metastatic disease and/or death, research is ongoing to improve salvage systemic therapy. Prostate-specific membrane antigen (PSMA) is highly overexpressed by the majority of prostate cancers. While initial methods of exploiting PSMA's high and selective expression were suboptimal, additional work in both imaging and therapeutics is progressing. Salvage therapy and imaging modalities in this setting are briefly reviewed, and the rationale for PSMA-based systemic salvage radioimmunotherapy is described.

1. Prostate-Specific Antigen and Biochemical Relapse

Clinically localized prostate cancer (PC) may have a variable, often protracted course from first diagnosis to metastasis [1, 2]. Despite recent controversies, prostate-specific antigen (PSA) has not only revolutionized diagnosis but is also used to monitor disease recurrence after primary treatment options such as radical prostatectomy (RP) or local definitive radiotherapy (RT). An important aspect of monitoring is the concept of biochemical recurrence (BCR) which can be defined within the framework of PSA. A primary definition had proven elusive as there are considerable differences between the primary therapies in regards to their PSA kinetics [3]. Following prostatectomy, absolute PSA values of 0.2–0.4 ng/mL are commonly used to define BCR, with a PSA of 0.4 ng/mL followed by another increase suggested for inclusion in clinical trials for men with BCR following RP [4, 5]. In the post-RT setting, an increase of 2 ng/mL from the patients' post-RT nadir is used as the marker for recurrent/persistent disease (biochemical failure) [6].

In many parts of the world, the majority of men diagnosed with PC are usually well suited for local curative attempts with RP or RT. In this population it has been shown that BCR occurs in 12–42% [7] and 22–69% [8], respectively, overall approximating 30% of patients treated with local

therapy for curative intent [5, 9, 10]. In the United States alone, it is estimated that approximately 50,000 patients are diagnosed with BCR annually [4, 11].

2. Salvage Therapy: Local Options

Once these patients experience BCR, the decision to start secondary or salvage therapy is a process for which may be as complicated as the decision about primary therapy. As at initial diagnosis, the range of outcomes after BCR is variable, with some men progressing to overt metastatic disease and death despite therapy and others dying of other causes even without further PC intervention [12]. As a concept akin to other solid tumors, those with local recurrence might be cured with local therapy; some with systemic recurrence may benefit from systemic therapy, though as with other solid tumors in general, only those with local recurrence tend to be cured with salvage therapy. There are many options that include salvage RP, brachytherapy, external beam radiation therapy, cryotherapy, androgen deprivation therapy (ADT), or a combination of these modalities.

For those with BCR following radiation therapy, salvage radical prostatectomy (SRP) after primary radiotherapy can offer an effective management option. Eastham and colleagues studied 146 patients who underwent SRP for biopsy-proven local recurrence of PC [13]. In this study BCR was defined as a serum PSA of 0.2 ng/mL or higher or the initiation of androgen deprivation therapy after radiotherapy. Over a period of 5 years the recurrence-free probability was 54%, and only one patient experienced a clinical local recurrence, with a 5-year cumulative incidence of death from PC of 4%. As all of the prior reported experience was retrospective, the Cancer and Leukemia Group B (CALGB) performed a multicenter prospective study of SRP in patients who had BCR after radiotherapy. In this study of 41 patients, the 5-year biochemical-free survival was 55% and overall survival (OS) was 85% [14]. The time to first incontinent-free rates at 3, 6, and 12 months after surgery were 90%, 18%, and 9%, and time to first erectile dysfunction-free rates following SRP at 3, 6, and 12 months were 87%, 25%, and 14%. Despite these potentially encouraging efficacy results, SP is currently reserved for a highly select population based upon a number of factors, including real and/or perceived toxicity.

Salvage cryotherapy is an option which some see as less invasive approach to surgery with fewer side effects in the absence of prospective randomized studies. A retrospective analysis examined 76 patients over a 10-year period with a mean Gleason score of 7, who had prostate cryotherapy as salvage therapy before January 1999. At the end of this study, 43 of 76 men (56.6%) were still alive; 33 men (43.4%) had died but only 13.2% from prostate cancer and 22.4% from noncancerous causes, and 6.6% died from unknown causes [15]. A pooled analysis of salvage cryoablation demonstrated 54.5% 5-year actuarial biochemical disease-free survival with an incontinence rate of 4.4% and rectal fistula rate of 1.2% [16]. These and other investigators have concluded that cryosurgery is safe and effective treatment in selected patients in whom radiation therapy fails [15–17]. Further study is necessary, including improvement and standardization of technique.

One option commonly offered to patients with BCR after primary RP is salvage radiation therapy (SRT). Most of the available data comes from retrospective series. Stephenson et al. analyzed data from 17 tertiary care centers, evaluating 1540 patients. The six-year progression-free probability was 32% overall, 48% for patients with a pre-SRT PSA less than or equal to 0.5, 40% with a PSA > 0.5–1, 28% for patients with a PSA 1–1.5, and 18% for PSA greater than 1.5. These findings suggest that delivering SRT at the earliest sign of recurrence, when the PSA is low, is optimal, as nearly half of patients may have a long-term PSA response, including some with other unfavorable prognostic factors, including a PSA doubling time of 10 months or less or with poorly differentiated (Gleason 8–10) histology. A nomogram is available utilizing independently significant variables, including PSA level before SRT, prostatectomy Gleason score, PSA doubling time, surgical margins, androgen-deprivation therapy before or during RT therapy, and lymph node metastasis [18].

A retrospective review from Johns Hopkins included 635 men who previously underwent RP and were subsequently observed (63%), underwent SRT (25%), or SRT + hormonal therapy (12%) for either a biochemical or local recurrence. SRT was associated with a threefold increase in prostate cancer-specific survival (CSS) compared to those not treated with SRT (HR 0.32, $P < 0.001$). The addition of hormonal therapy did not improve CSS. Without long-term followup this benefit in CSS was limited to those with a doubling time of less than 6 months and persisted after adjustment for other prognostic factors. SRT delivered greater than two years after recurrence or, for those men whose PSA never became undetectable after RP, did not result in improvement in CSS at the time of analysis [19].

Although there are limitations in the evaluation of retrospective data, these reports provide solid evidence for the benefit of early SRT. Important factors to consider in determining the need for SRT include preoperative and pre-RT PSA, postrecurrence doubling time, pathologic features suggestive of a local recurrence (e.g., positive margins), achievement or nonachievement of a nondetectable PSA post-operatively, pattern of rise of PSA (whether or not consistent with a local recurrence), long recurrence interval from surgery, as well as patient factors [18, 20, 21].

3. Imaging in the Setting of Biochemical Relapse

One of the major issues with local therapy (whether for newly diagnosed clinically localized disease or in the setting of BCR) is the lack of ability to accurately determine the presence or absence of distant metastatic disease. It is likely that the most significant reason for failure of most attempts at salvage therapy for biochemically recurrent PC is the presence of undetected metastatic disease. Conventional imaging techniques such as transrectal ultrasonography, magnetic resonance imaging (MRI), computed tomography

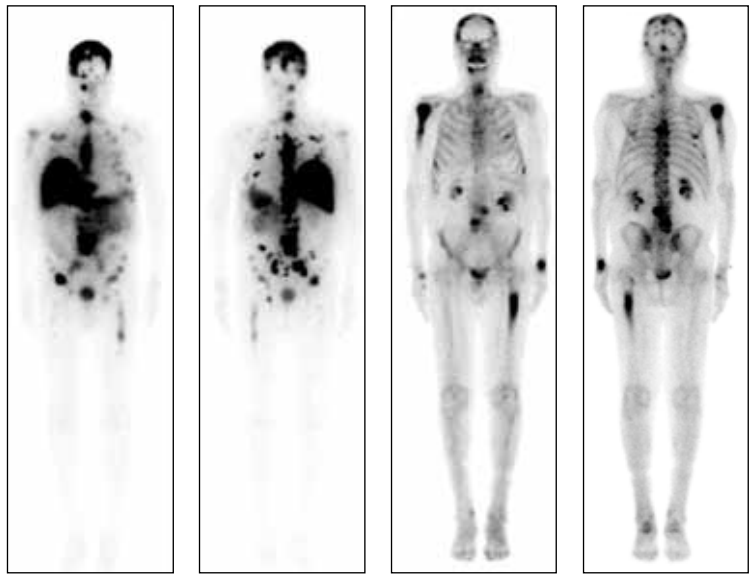

Figure 1: Anterior (a) and posterior (b) planar gamma camera images of radiolabeled J591. A greater number of lesions are apparent compared to anterior (c) and posterior (d) ^{99m}Tc-MDP bone scan. Hepatic clearance of radiolabeled mAb results in nonspecific uptake in the liver.

(CT), and ^{99}Tm-MDP scintigraphy (bone scan) are usually not sensitive or specific enough to detect metastatic or recurrent prostate disease [22–28]. Therefore, an increase in PSA may precede a clinically detectable recurrent pelvic or metastatic cancer by months to years [29].

Though initial attempts using monoclonal antibodies (mAbs) to PSA and PAP were unsuccessful [30], more recently various and more specific markers of PC have been identified, including cell surface proteins, glycoprotein, receptors, enzymes, and peptides [31]. Prostate-specific membrane antigen (PSMA) is the most well established, highly specific prostate epithelial cell membrane antigen known [32–36]. The first and only approved agent for targeting PSMA in PC is ^{111}In-capromab [37].

An initial study utilizing capromab pendetide in men BCR after prostatectomy and lymphadenectomy demonstrated safety [38]. Kahn et al. performed a study in 32 men with BCR after prostatectomy prior to SRT; 61% of those with evidence of local disease only had a durable response to SRT versus 28% with durable response if they had evidence of distant disease on ^{111}In-capromab imaging [39]. However, while additional similar studies support these results [40], others have demonstrated no benefit with the use of capromab pendetide in selection of patients for local salvage therapy [41, 42]. Some efforts to improve ^{111}In-capromab imaging have added SPECT/CT fusion imaging, but results remain suboptimal [43–45].

A major reason for the suboptimal results with capromab pendetide lies with its targeting of the internal domain of PSMA, leading to the inability to bind to viable cells [32–35, 46]. Recognition of these features led to the development of mAbs by Bander et al. to the exposed, extracellular domain of PSMA [46–48]. J591, a deimmunized mAb against the extracellular domain of PSMA, has been the lead clinical candidate [48, 49]. While no formal prostate imaging studies of J591 have been conducted, several therapeutic studies examining the clinical utility of radiolabeled J591 have been performed with built-in imaging components [49–51]. Radiolabeled J591 has successfully targeted (imaged) 89–100% osseous targeting and 69–100% soft tissue targeting [49–51], including cases where J591 demonstrated lesions that were not apparent on the bone scan but were identified on subsequent MR or conventional imaging as the lesion progressed (Figure 1) [52]. Current imaging work with anti-PSMA mAbs involves immune-PET imaging [53, 54]. Additional studies utilize small molecule inhibitors, including ^{123}I-MIP-1072, ^{123}I-MIP-1095, ^{99m}Tc-MIP-1404, and ^{99m}Tc-MIP-1405 [55, 56].

4. Systemic Therapy for Biochemical Relapse

The addition of hormonal therapy to primary RT has led to improvements for some men with clinically localized PC, possibly by radiosensitization and/or treating micrometastatic disease. This might be true with SRT as well, with several retrospective studies supporting this concept [57, 58]. Initial results of a large, prospective randomized study, RTOG 9601, in which SRT was compared with SRT + bicalutamide in patients with an elevated PSA after prostatectomy have been presented [57]. With a median followup of seven years, a statistically significant improvement in freedom from PSA progression with adjuvant bicalutamide versus RT alone has been reported (57 versus 40%) as well as incidence of metastatic disease (7 versus 13%). RTOG 0534, a Phase III Trial of short-term androgen deprivation with pelvic lymph node or prostate bed only

radiotherapy (SPPORT) in PC patients with a rising PSA after RP, is currently accruing (http://www.clinicaltrials.gov/ NCT00567580). Patients are randomly assigned to one of three arms: prostate bed RT only, prostate bed RT + neoadjuvant and concurrent ADT, or RT to the prostate bed and pelvic lymph nodes with neoadjuvant and concurrent ADT [59]. This study will help address the utility of the addition of ADT to SRT.

Though good local salvage options exist, not all patients qualify or agree to receive them, and most suffer disease progression despite local salvage therapy, likely because of micrometastatic disease outside of the prostate/prostate bed and pelvis that is not apparent on conventional imaging. Therefore systemic therapy is often employed. The most common management option for BCR after local therapy is ADT. While many studies have demonstrated that ADT does not prolong time to metastases and death in all comers, there are subgroups that likely benefit. Higher-grade disease and poorer PSA kinetics (i.e., short PSA doubling time) may predict improvement in outcome with early ADT [60, 61]. Additional evidence to support early ADT stems from the high-risk clinically localized or locally advanced settings [62–64]. However, while ADT may lead to some improvements, toxicity exists [65–70], and it is not curative in this situation. Chemotherapy is proven to improve survival and patient-reported outcomes in late stage disease but, as in most advanced solid tumors, is not able to overcome bulky disease and leads to cures in that setting [71, 72]. The addition of chemotherapy at an earlier stage has demonstrated a survival benefit in many solid tumors (i.e., neoadjuvant or adjuvant chemotherapy in combination with surgery/radiotherapy), presumably by eradicating micrometastatic sites of disease. We await the results of a study examining the use of chemotherapy in combination with hormonal therapy to treat micrometastatic disease in men with BCR after prostatectomy (http://www.clinicaltrials.gov/ NCT00514917) [73].

5. Prostate-Specific Membrane Antigen-Based Radioimmunotherapy

As discussed above, the concept of systemic therapy to eliminate micrometastatic disease has merit. "Targeted therapy" is designed to deliver agents to malignant cells and spare normal cells. PSMA is an ideal target for prostate cancer, based upon its near universal expression in PC. While the initial observations were that expression was limited to prostate cells, it is now known that there are low levels of expression in other tissues, including brush border of small intestine, renal proximal tubule lumen, and salivary glands. However, levels of expression are greatly increased in prostate cancer (as opposed to benign prostatic epithelial cells) and increase with grade, stage, and hormonal therapy [32–35]. Furthermore, alternative sites with low levels of expression have minimal or no exposure to circulating mAb, as they are protected by basement membranes and their luminal surface site of expression. Several studies have demonstrated the ability of radiolabeled J591 to target and treat metastatic castration-resistant prostate cancer (CRPC).

Two independent phase I radioimmunotherapy (RIT) trials were performed using Yttrium-90 (^{90}Y) or Lutetium-177 (^{177}Lu) linked via a DOTA chelate to J591 in patients with metastatic CRPC. These trials defined the MTD and further refined dosimetry, pharmacokinetics, and immunogenicity (HAHA) of the radiolabeled mAb with some efficacy seen [50, 51]. Additional phase I and phase II studies utilizing ^{177}Lu-J591 have confirmed the ability of J591 to successfully target various sites of metastatic prostate cancer with the majority of subjects receiving full doses of radiolabeled antibody experiencing PSA declines and some measurable disease responses demonstrated [49, 74, 75]. As expected with radioimmunotherapy in general, dose-limiting toxicity is reversible myelosuppression, with a minority of patients also experiencing mAb-related infusion reactions (without pre-medication) or transient grade 1 transaminitis [49–51, 74–76].

Based on the physical properties of radionuclides, differential responses are expected depending upon radionuclide and tumor properties. ^{177}Lu is a low energy β emitter best for lesions 1–3 mm in diameter, while the higher β energy of ^{90}Y is best suited for 28–42 mm lesions [77]. An initial review of J591 RIT validated these properties in the clinical CRPC setting [76]. This leads to the hypothesis that ^{177}Lu-J591 should be less effective in the bulky metastatic CRPC setting but may lead to significantly more benefit in a micrometastatic disease setting. Indeed, RIT in general may have a higher impact in the minimal disease setting [78–80].

Prostate cancer is a radiosensitive disease, and BCR is common. Salvage local therapy may be successful but does not address disease sites outside of the prostate bed/pelvis, and most patients ultimately progress. Nearly all PC overexpresses PSMA; J591 is able to target metastatic disease sites. Full length anti-PSMA mAb has minimal to no access to other sites of low-level PSMA expression. Anti-PSMA-based RIT has demonstrated efficacy, and ^{177}Lu is optimal for 1–3 mm (i.e., micrometastatic) lesions.

Enrollment is ongoing in a multicenter Department of Defense and Prostate Cancer Foundation-sponsored study testing the concept of salvage targeted anti-PSMA-based RIT (http://www.clinicaltrials.gov/ NCT00859781). Men with high-risk CRPC (PSA doubling time <8 months and/or PSA > 20 [73]) and no evidence of disease on CT/MRI and bone scans are randomized in a 2 : 1 fashion to receive double-blinded ^{177}Lu-J951 versus ^{111}In-J591 (control) with a backbone of hormonal therapy (ketoconazole and hydrocortisone) and will undergo planar gamma camera imaging with SPECT following infusion. The primary endpoint of the study is 18-month metastasis-free survival with additional endpoints of median metastasis-free survival and overall survival. Secondary/exploratory endpoints include evaluation of radiolabeled J591 imaging to detect sites of metastases not apparent on standard CT/MRI and bone scan, validation of adrenal androgen levels as biomarkers for ketoconazole [81], and analysis of circulating tumor cells captured via CellSearch methodology as well as PSMA-GEDI capture [82] for PSMA expression and counts to predict the appearance of radiographic metastases.

6. Conclusions

Biochemical relapse after local therapy for prostate cancer is common. While local salvage therapy is available, deficiencies in imaging currently lead to difficulties in selecting appropriate patients. For those with microscopic sites of disease outside of the prostate/prostate bed, targeted systemic salvage therapy is appealing. Prostate-specific membrane antigen-based diagnostics and therapeutics may lead to improvements in this disease setting.

Authors' Contribution

S. Kosuri and N. Akhtar contributed equally to this paper.

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References

[1] M. J. Zelefsky et al., "Cancer of the prostate," in *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*, V. T. DeVita Jr. et al., Ed., vol. 1, pp. 1392–1452, Lippincott Williams & Wilkins, Philadelphia, Pa, USA, 8th edition, 2008.

[2] A. L. Potosky, B. B. Reeve, L. X. Clegg et al., "Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy," *Journal of the National Cancer Institute*, vol. 94, no. 6, pp. 430–437, 2002.

[3] A. J. Stephenson, M. W. Kattan, J. A. Eastham et al., "Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition," *Journal of Clinical Oncology*, vol. 24, no. 24, pp. 3973–3978, 2006.

[4] H. I. Scher, M. Eisenberger, A. V. D'Amico et al., "Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendations from the Prostate-Specific Antigen Working Group," *Journal of Clinical Oncology*, vol. 22, no. 3, pp. 537–556, 2004.

[5] K. R. Han, J. K. Cohen, R. J. Miller et al., "Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicenter experience," *Journal of Urology*, vol. 170, no. 4, part 1, pp. 1126–1130, 2003.

[6] M. Roach, G. Hanks, H. Thames Jr. et al., "Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference," *International Journal of Radiation Oncology Biology Physics*, vol. 65, no. 4, pp. 965–974, 2006.

[7] M. A. Khan, M. Han, A. W. Partin, J. I. Epstein, and P. C. Walsh, "Long-term cancer control of radical prostatectomy in men younger than 50 years of age: update 2003," *Urology*, vol. 62, no. 1, pp. 86–92, 2003.

[8] W. U. Shipley, H. D. Thames, H. M. Sandler et al., "Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis," *JAMA*, vol. 281, no. 17, pp. 1598–1604, 1999.

[9] A. L. Zietman, C. S. Chung, J. J. Coen, and W. U. Shipley, "10-Year outcome for men with localized prostate cancer treated with external radiation therapy: results of a cohort study," *Journal of Urology*, vol. 171, no. 1, pp. 210–214, 2004.

[10] P. K. Agarwal, N. Sadetsky, B. R. Konety, M. I. Resnick, and P. R. Carroll, "Treatment failure after primary and salvage therapy for prostate cancer: likelihood, patterns of care, and outcomes," *Cancer*, vol. 112, no. 2, pp. 307–314, 2008.

[11] S. J. Freedland and J. W. Moul, "Prostate specific antigen recurrence after definitive therapy," *Journal of Urology*, vol. 177, no. 6, pp. 1985–1991, 2007.

[12] S. J. Freedland, E. B. Humphreys, L. A. Mangold et al., "Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy," *JAMA*, vol. 294, no. 4, pp. 433–439, 2005.

[13] P. Paparel, A. M. Cronin, C. Savage, P. T. Scardino, and J. A. Eastham, "Oncologic outcome and patterns of recurrence after salvage radical prostatectomy," *European Urology*, vol. 55, no. 2, pp. 404–411, 2009.

[14] M. H. Sokoloff, G. D. Steinberg, S. Halabi et al., "Management of recurrent prostate cancer after radiotherapy: results from CALGB 9687," in *Proceedings of the Annual Meeting of the American Urological Association (AUA '08)*, A Contemporary Prospective Multi-Institutional Salvage Radical Prostatectomy Series, May 2008.

[15] P. Cheetham, M. Truesdale, S. Chaudhury, S. Wenske, G. W. Hruby, and A. Katz, "Long-term cancer-specific and overall survival for men followed more than 10 years after primary and salvage cryoablation of the prostate," *Journal of Endourology*, vol. 24, no. 7, pp. 1123–1129, 2010.

[16] L. L. Pisters, J. C. Rewcastle, B. J. Donnelly, F. M. Lugnani, A. E. Katz, and J. S. Jones, "Salvage prostate cryoablation: initial results from the cryo on-line data registry," *Journal of Urology*, vol. 180, no. 2, pp. 559–564, 2008.

[17] P. E. Spiess, A. E. Katz, J. L. Chin et al., "A pretreatment nomogram predicting biochemical failure after salvage cryotherapy for locally recurrent prostate cancer," *BJU International*, vol. 106, no. 2, pp. 194–198, 2010.

[18] A. J. Stephenson, P. T. Scardino, M. W. Kattan et al., "Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy," *Journal of Clinical Oncology*, vol. 25, no. 15, pp. 2035–2041, 2007.

[19] B. J. Trock, M. Han, S. J. Freedland et al., "Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy," *JAMA*, vol. 299, no. 23, pp. 2760–2769, 2008.

[20] A. J. Stephenson, S. F. Shariat, M. J. Zelefsky et al., "Salvage Radiotherapy for Recurrent Prostate Cancer after Radical Prostatectomy," *JAMA*, vol. 291, no. 11, pp. 1325–1332, 2004.

[21] S. E. Cotter, M. H. Chen, J. W. Moul et al., "Salvage radiation in men after prostate-specific antigen failure and the risk of death," *Cancer*, vol. 117, no. 17, pp. 3925–3932, 2011.

[22] P. H. Smith, A. Bono, F. Calais da Silva et al., "Some limitations of the radioisotope bone scan in patients with metastatic prostatic cancer: a subanalysis of EORTC trial 30853," *Cancer*, vol. 66, no. 5, supplement, pp. 1009–1016, 1990.

[23] F. Parivar, H. Hricak, K. Shinohara et al., "Detection of locally recurrent prostate cancer after cryosurgery: evaluation by transrectal ultrasound, magnetic resonance imaging, and three- dimensional proton magnetic resonance spectroscopy," *Urology*, vol. 48, no. 4, pp. 594–599, 1996.

[24] K. K. Yu and H. Hricak, "Imaging prostate cancer," *Radiologic Clinics of North America*, vol. 38, no. 1, pp. 59–85, 2000.

[25] J. Kurhanewicz, D. B. Vigneron, R. G. Males, M. G. Swanson,

K. K. Yu, and H. Hricak, "The prostate: MR imaging and spectroscopy: present and future," *Radiologic Clinics of North America*, vol. 38, no. 1, pp. 115–138, 2000.

[26] D. M. Nudell, A. E. Wefer, H. Hricak, and P. R. Carroll, "Imaging for recurrent prostate cancer," *Radiologic Clinics of North America*, vol. 38, no. 1, pp. 213–229, 2000.

[27] F. May, T. Treumann, P. Dettmar, R. Hartung, and J. Breul, "Limited value of endorectal magnetic resonance imaging and transrectal ultrasonography in the staging of clinically localized prostate cancer," *BJU International*, vol. 87, no. 1, pp. 66–69, 2001.

[28] H. Hricak, H. Schöder, D. Pucar et al., "Some limitations of the radioisotope bone scan in patients with metastatic prostatic cancer. A subanalysis of EORTC trial 30853. the EORTC urological group," *Seminars in Oncology*, vol. 30, no. 5, supplement, pp. 616–634, 2003.

[29] C. R. Pound, A. W. Partin, M. A. Eisenberger, D. W. Chan, J. D. Pearson, and P. C. Walsh, "Natural history of progression after PSA elevation following radical prostatectomy," *JAMA*, vol. 281, no. 17, pp. 1591–1597, 1999.

[30] A. Ghosh and W. D. W. Heston, "Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer," *Journal of Cellular Biochemistry*, vol. 91, no. 3, pp. 528–539, 2004.

[31] J. S. Ross, K. E. Gray, I. J. Webb et al., "Antibody-based therapeutics: focus on prostate cancer," *Cancer and Metastasis Reviews*, vol. 24, no. 4, pp. 521–537, 2005.

[32] J. S. Horoszewicz, E. Kawinski, and G. P. Murphy, "Monoclonal antibodies to a new antigenic marker in epithelial prostatic cells and serum of prostatic cancer patients," *Anticancer Research*, vol. 7, no. 5, pp. 927–935, 1987.

[33] R. S. Israeli, C. T. Powell, W. R. Fair, and W. D. W. Heston, "Molecular cloning of a complementary DNA encoding a prostate-specific membrane antigen," *Cancer Research*, vol. 53, no. 2, pp. 227–230, 1993.

[34] R. S. Israeli, C. T. Powell, J. G. Corr, W. R. Fair, and W. D. W. Heston, "Expression of the prostate-specific membrane antigen," *Cancer Research*, vol. 54, no. 7, pp. 1807–1811, 1994.

[35] J. K. Troyer, M. L. Beckett, and G. L. Wright, "Detection and characterization of the prostate-specific membrane antigen (PSMA) in tissue extracts and body fluids," *International Journal of Cancer*, vol. 62, no. 5, pp. 552–558, 1995.

[36] R. Sokoloff, K. C. Norton, C. L. Gasior, K. M. Marker, and L. S. Grauer, "A dual-monoclonal sandwich assay for prostate-specific membrane antigen: levels in tissues, seminal fluid and urine," *Prostate*, vol. 43, no. 2, pp. 150–157, 2000.

[37] U. Elsässer-Beile, P. Wolf, D. Gierschner, P. Bühler, W. G. Schultze-Seemann, and U. Wetterauer, "A new generation of monoclonal and recombinant antibodies against cell-adherent prostate specific membrane antigen for diagnostic and therapeutic targeting of prostate cancer," *Prostate*, vol. 66, no. 13, pp. 1359–1370, 2006.

[38] D. B. Sodee, R. Conant, M. Chalfant et al., "Preliminary imaging results using In-111 labeled CYT-356 (Prostascint(TM)) in the detection of recurrent prostate cancer," *Clinical Nuclear Medicine*, vol. 21, no. 10, pp. 759–767, 1996.

[39] D. Kahn, R. D. Williams, M. J. Manyak et al., "111Indium-capromab pendetide in the evaluation of patients with residual or recurrent prostate cancer after radical prostatectomy," *Journal of Urology*, vol. 159, no. 6, pp. 2041–2047, 1998.

[40] P. E. Levesque, P. T. Nieh, L. N. Zinman, D. W. Seldin, and J. A. Libertino, "Radiolabeled monoclonal antibody indium 111-labeled CYT-356 localizes extraprostatic recurrent carcinoma after prostatectomy," *Urology*, vol. 51, no. 6, pp. 978–984, 1998.

[41] S. Wilkinson and G. Chodak, "The role of111indium-capromab pendetide imaging for assessing biochemical failure after radical prostatectomy," *Journal of Urology*, vol. 172, no. 1, pp. 133–136, 2004.

[42] C. T. Thomas, P. T. Bradshaw, B. H. Pollock et al., "Indium-111-capromab pendetide radioimmunoscintigraphy and prognosis for durable biochemical response to salvage radiation therapy in men after failed prostatectomy," *Journal of Clinical Oncology*, vol. 21, no. 9, pp. 1715–1721, 2003.

[43] R. J. Ellis, E. Y. Kim, R. Conant et al., "Radioimmunoguided imaging of prostate cancer foci with histopathological correlation," *International Journal of Radiation Oncology Biology Physics*, vol. 49, no. 5, pp. 1281–1286, 2001.

[44] J. K. DeWyngaert, M. E. Noz, B. Ellerin, E. L. Kramer, G. Q. Maguire, and M. P. Zeleznik, "Procedure for unmasking localization information from ProstaScint scans for prostate radiation therapy treatment planning," *International Journal of Radiation Oncology Biology Physics*, vol. 60, no. 2, pp. 654–662, 2004.

[45] C. J. Schettino, E. L. Kramer, M. E. Noz, S. Taneja, P. Padmanabhan, and H. Lepor, "Impact of fusion of indium-111 capromab pendetide volume data sets with those from MRI of CT in patients with recurrent prostate cancer," *American Journal of Roentgenology*, vol. 183, no. 2, pp. 519–524, 2004.

[46] H. Liu, P. Moy, S. Kim et al., "Monoclonal antibodies to the extracellular domain of prostate-specific membrane antigen also react with tumor vascular endothelium," *Cancer Research*, vol. 57, no. 17, pp. 3629–3634, 1997.

[47] H. Liu, A. K. Rajasekaran, P. Moy et al., "Constitutive and antibody-induced internalization of prostate-specific membrane antigen," *Cancer Research*, vol. 58, no. 18, pp. 4055–4060, 1998.

[48] N. H. Bander, E. J. Trabulsi, L. Kostakoglu et al., "Targeting metastatic prostate cancer with radiolabeled monoclonal antibody J591 to the extracellular domain of prostate specific membrane antigen," *Journal of Urology*, vol. 170, no. 5, pp. 1717–1721, 2003.

[49] S. T. Tagawa, H. Beltran, S. Vallabhajosula et al., "Anti-prostate-specific membrane antigen-based radioimmunotherapy for prostate cancer," *Cancer*, vol. 116, no. 4, supplement, pp. 1075–1083, 2010.

[50] N. H. Bander, M. I. Milowsky, D. M. Nanus, L. Kostakoglu, S. Vallabhajosula, and S. J. Goldsmith, "Phase I trial of 177Lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer," *Journal of Clinical Oncology*, vol. 23, no. 21, pp. 4591–4601, 2005.

[51] M. I. Milowsky, D. M. Nanus, L. Kostakoglu, S. Vallabhajosula, S. J. Goldsmith, and N. H. Bander, "Phase I trial of yttrium-90-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for androgen-independent prostate cancer," *Journal of Clinical Oncology*, vol. 22, no. 13, pp. 2522–2531, 2004.

[52] N. H. Bander, "Technology Insight: monoclonal antibody imaging of prostate cancer," *Nature Clinical Practice Urology*, vol. 3, no. 4, pp. 216–225, 2006.

[53] J. P. Holland, V. Divilov, N. H. Bander, P. M. Smith-Jones, S. Larson, and J. S. Lewis, "89Zr-DFO-J591 for immunoPET of prostate-specific membrane antigen expression in vivo," *Journal of Nuclear Medicine*, vol. 51, no. 8, pp. 1293–1300, 2010.

[54] M. J. Evans, P. M. Smith-Jones, J. Wongvipat et al., "Non-invasive measurement of androgen receptor signaling with a

positron-emitting radiopharmaceutical that targets prostate-specific membrane antigen," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 23, pp. 9578–9582, 2011.

[55] R. E. Coleman, J. B. Stubbs, J. A. Barrett, M. De La Guardia, N. Lafrance, and J. W. Babich, "Radiation dosimetry, pharmacokinetics, and safety of ultratrace iobenguane I-131 in patients with malignant pheochromocytoma/paraganglioma or metastatic carcinoid," *Cancer Biotherapy and Radiopharmaceuticals*, vol. 24, no. 4, pp. 469–475, 2009.

[56] J. R. Osborne, N. H. Akhtar, S. Vallabhajosula et al., "Tc-99m labeled small-molecule inhibitors of prostate-specific membrane antigen (PSMA): new molecular imaging probes to detect metastatic prostate adenocarcinoma (PC)," *Journal of Clinical Oncology*, vol. 30, supplement 5, 2012, Abstract no. 173.

[57] C. R. King and M. T. Spiotto, "Improved outcomes with higher doses for salvage radiotherapy after prostatectomy," *International Journal of Radiation Oncology Biology Physics*, vol. 71, no. 1, pp. 23–27, 2008.

[58] R. Cheung, S. L. Tucker, A. L. Lee et al., "Assessing the impact of an alternative biochemical failure definition on radiation dose response for high-risk prostate cancer treated with external beam radiotherapy," *International Journal of Radiation Oncology Biology Physics*, vol. 61, no. 1, pp. 14–19, 2005.

[59] A Phase III Trial of Short Term Androgen Deprivation With Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPPORT) in Prostate Cancer Patients With a Rising PSA After Radical Prostatectomy—NCT00567580, 2007, http://clinicaltrials.gov/ct2/show/NCT00567580.

[60] J. W. Moul, "Prostate specific antigen only progression of prostate cancer," *Journal of Urology*, vol. 163, no. 6, pp. 1632–1642, 2000.

[61] C. J. Ryan and E. J. Small, "High risk biochemical relapse and the timing of androgen deprivation therapy," *Journal of Urology*, vol. 176, no. 6, part 2, pp. S61–S65, 2006.

[62] C. A. Lawton, K. Winter, D. Grignon, and M. V. Pilepich, "Androgen suppression plus radiation versus radiation alone for patients with stage D_1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85–31," *Journal of Clinical Oncology*, vol. 23, no. 4, pp. 800–807, 2005.

[63] E. M. Messing, J. Manola, M. Sarosdy, G. Wilding, E. D. Crawford, and D. Trump, "Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer," *The New England Journal of Medicine*, vol. 341, no. 24, pp. 1781–1788, 1999.

[64] T. B. Dorff, T. W. Flaig, C. M. Tangen et al., "Adjuvant androgen deprivation for high-risk prostate cancer after radical prostatectomy: SWOG S9921 study," *Journal of Clinical Oncology*, vol. 29, no. 15, pp. 2040–2045, 2011.

[65] J. C. Smith, S. Bennett, L. M. Evans et al., "The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer," *The Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 9, pp. 4261–4267, 2001.

[66] M. R. Smith, J. S. Finkelstein, F. J. McGovern et al., "Changes in body composition during androgen deprivation therapy for prostate cancer," *The Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 2, pp. 599–603, 2002.

[67] M. Braga-Basaria, A. S. Dobs, D. C. Muller et al., "Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy," *Journal of Clinical Oncology*, vol. 24, no. 24, pp. 3979–3983, 2006.

[68] S. Basaria, D. C. Muller, M. A. Carducci, J. Egan, and A. S. Dobs, "Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy," *Cancer*, vol. 106, no. 3, pp. 581–588, 2006.

[69] M. R. Smith, H. Lee, and D. M. Nathan, "Insulin sensitivity during combined androgen blockade for prostate cancer," *The Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 4, pp. 1305–1308, 2006.

[70] N. L. Keating, A. J. O'Malley, and M. R. Smith, "Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer," *Journal of Clinical Oncology*, vol. 24, no. 27, pp. 4448–4456, 2006.

[71] I. F. Tannock, R. De Wit, W. R. Berry et al., "Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer," *The New England Journal of Medicine*, vol. 351, no. 15, pp. 1502–1512, 2004.

[72] D. P. Petrylak, C. M. Tangen, M. H. A. Hussain et al., "Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer," *The New England Journal of Medicine*, vol. 351, no. 15, pp. 1513–1520, 2004.

[73] A Randomized, Open Label, Multicenter, Phase III, 2-Arm Study of Androgen Deprivation With Leuprolide, +/- Docetaxel for Clinically Asymptomatic Prostate Cancer Subjects With a Rising PSA Following Definitive Local Therapy—NCT00514917, 2007, http://clinicaltrials.gov/ct2/show/NCT00514917.

[74] S. T. Tagawa, M. I. Milowsky, M. Morris et al., "Phase II trial of 177Lutetium radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (177Lu-J591) in patients (pts) with metastatic castrate-resistant prostate cancer (metCRPC)," *Journal of Clinical Oncology*, vol. 26, article 284s, 2008, Abstract no. 5140.

[75] S. T. Tagawa, S. Vallabhajosula, J. Osborne et al., "Phase I trial of fractionated-dose ^{177}lutetium radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) in patients (pts) with metastatic castration-resistant prostate cancer (metCRPC)," *Journal of Clinical Oncology*, vol. 28, supplement 15, 2010, Abstract no. 4667.

[76] N. H. Akhtar, D. M. Nanus, J. Osborne et al., "Anti-prostate specific membrane antigen (PSMA)-based radioimmunotherapy: a combined analysis of radiolabeled-J591 studies," *Journal of Clinical Oncology*, vol. 29, supplement 7, 2011, Abstract no. 136.

[77] J. A. O'Donoghue, G. Sgouros, C. R. Divgi, and J. L. Humm, "Single-dose versus fractionated radioimmunotherapy: model comparisons for uniform tumor dosimetry," *Journal of Nuclear Medicine*, vol. 41, no. 3, pp. 538–547, 2000.

[78] M. S. Kaminski, M. Tuck, J. Estes et al., "131I-tositumomab therapy as initial treatment for follicular lymphoma," *The New England Journal of Medicine*, vol. 352, no. 5, pp. 441–449, 2005.

[79] J. P. Leonard, M. Coleman, L. Kostakoglu et al., "Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I 131 tositumomab for untreated follicular lymphoma," *Journal of Clinical Oncology*, vol. 23, no. 24, pp. 5696–5704, 2005.

[80] O. W. Press, J. M. Unger, R. M. Braziel et al., "Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group protocol S9911," *Journal of Clinical Oncology*,

vol. 24, no. 25, pp. 4143–4149, 2006.

[81] C. J. Ryan, S. Halabi, S. S. Ou, N. J. Vogelzang, P. Kantoff, and E. J. Small, "Adrenal androgen levels as predictors of outcome in prostate cancer patients treated with ketoconazole plus antiandrogen withdrawal: results from a Cancer and Leukemia Group B study," *Clinical Cancer Research*, vol. 13, no. 7, pp. 2030–2037, 2007.

[82] J. P. Gleghorn, E. D. Pratt, D. Denning et al., "Capture of circulating tumor cells from whole blood of prostate cancer patients using geometrically enhanced differential immunocapture (GEDI) and a prostate-specific antibody," *Lab on a Chip*, vol. 10, no. 1, pp. 27–29, 2010.

Weill Cornell Medical College

Rosemary Kraemer, Ph.D.
Director, Human Research Protections Programs
Division of Research Integrity
Research and Sponsored Programs
407 East 61st Street, 1st Floor
New York, New York 10065

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July 27, 2012

Scott T. Tagawa, MD
Assistant Professor

Submission Type: Expedited Amendment

Protocol Number: 0810010067

Protocol Title: A Randomized Phase 2 Trial of Lu Radiolabeled Monoclonal Antibody HuJ591 (Lu-J591) and ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy.

Nature of Amendment:
- WCMC Protocol, version 6 dated July 2, 2012
- Revised Informed Consent Form dated July 2, 2012
- Addition of FACT-P Questionnaire
- HIPAA Authorization Form

IRB Approval Date: July 26, 2012

Dear Dr. Tagawa:

The Institutional Review Board (IRB) has conducted an expedited review and approved the amendment to the abovementioned protocol.

Please do not hesitate to contact the IRB office staff if you have any questions or need assistance in complying with the terms of this approval.

Sincerely,

Rosemary Kraemer

Rosemary Kraemer, Ph.D.
Director, Human Research Protections Program

Please note the following important information about this approval:
- Billing Compliance: This approval is contingent upon continued adherence with institutional billing compliance policies.
- Information about the WCMC IRBs: The Weill Cornell Medical College (WCMC) Institutional Review Board (IRB) is constituted as required by the Federal Office for Human Research Protections (OHRP). WCMC holds a Federalwide Assurance (FWA) with OHRP. The FWA number is FWA00000093. The

WCMC IRB is registered on that FWA. The registration number for the IRB is: IRB #1 IRB00000952; and IRB #2 IRB00004327. Should you need additional information about the terms of the WCMC FWA or the WCMC IRB, please refer to
http://weill.cornell.edu/research/research_integrity/institutional_review_board/index.html

Weill Cornell Medical College

Data Safety Monitoring Board
407 East 61st Street, RR-110
New York, New York 10065

Telephone: 646-962-8192
E-mail: dsmb@med.cornell.edu
weill.cornell.edu/research/research_integrity/DSMB.html

Date: June 5, 2012

To: Scott Tagawa, M.D..

From: Marcus Reidenberg, M.D.
DSMB Chairman

Re: DSMB Review
Protocol: #0810010067
Title: A Randomized Phase 2 Trial of 177Lu Radiolabeled Monoclonal Antibody HuJ591 (177Lu-J591) and ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy

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The Weill Cornell Medical College ("WCMC") Data Safety Monitoring Board ("DSMB") has conducted a review of the following documentation:

- **DSMB Memo - Initial J591 Keto Analysis**

The DSMB requires no further documentation at this time and has retained this information in its files.

Thank you for your submission to the WCMC DSMB. Should you require any assistance, please contact us by emailing dsmb@med.cornell.edu or calling Lauren Odynocki, C.I.P., Research Integrity Coordinator, at (646) 962-8192.

Thank you.

TO: Omer Kucuk, MD
Principal Investigator
Hematology and Medical Oncology

DATE: September 21, 2011

RE: **Full Board Approval**
IRB00049135
A Randomized Phase 2 Trial of 177Lu Radiolabeled Monoclonal Antibody HuJ591 (177Lu-J591) and Ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy

Thank you for submitting a new application for this protocol. The Emory IRB reviewed it at its convened meeting on July 20, 2011 and granted approval effective from **7/20/2011** through **7/19/2012.** Thereafter, continuation of human subjects research activities requires the submission of another renewal application, which must be reviewed and approved by the IRB prior to the expiration date noted above. Please note carefully the following items with respect to this reapproval:

- Protocol version date: 5/25/2010
- Consent version date: 8/1/2011
- HIPAA version date: 6/20/2011
- Revocation Letter version date: 2/3/2011

Any reportable events (e.g., unanticipated problems involving risk to subjects or others, noncompliance, breaches of confidentiality, HIPAA violations, protocol deviations) must be reported to the IRB according to our Policies & Procedures at www.irb.emory.edu, immediately, promptly, or periodically. Be sure to check the reporting guidance and contact us if you have questions. Terms and conditions of sponsors, if any, also apply to reporting.

Before implementing any change to this protocol (including but not limited to sample size, informed consent, study design, you must submit an amendment request and secure IRB approval.

In future correspondence about this matter, please refer to the IRB file ID, name of the Principal Investigator, and study title. Thank you.

Sincerely,

Carla C. Belk, PhD, CIP
Sr Research Protocol Analyst
This letter has been digitally signed

CC:			
	Baker	Edith	Winship - Main
	Bryant	Toshiwa	Winship - Main
	Francis	Dixil	Winship - Main

Kithcart	Shelita	Winship - Main
Nguyen	Kim	Winship - Main
Sabzehi	Mehrdad	Winship - Main
Safavi	Farnoush	Winship - Main
Galt	James	Radiology - Main
Harris	Wayne B	Hematology and Medical Oncology
Jani	Ashesh	Radiation - Main
Lee	Daniel	Radiology - Main
Rossi	Peter	Radiation - Main
Schuster	David	Radiology - Main

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Office of Research Compliance and Quality Improvement, 8383 Wilshire Blvd. Suite 742, Beverly Hills, CA 90211

6/14/2012

To: EDWIN POSADAS
CC: JENNY JOAQUIN
From: Stephen Lim, M.D. Executive Chairperson
On Behalf of the CSMC Institutional Review Boards
Subject: IRB Approval for Pro00026955

Please note that the Cedars-Sinai Institutional Review Board (CSMC IRB) has approved you to conduct research involving human subjects. Please review the following information summarizing the approval granted:

IRB No.:	Pro00026955
Study Title:	WCMC J591: "A Randomized Phase 2 Trial of 177Lu Radiolabeled Monoclonal Antibody HuJ591 (177Lu-J591) and Ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy"
Approval Period:	**6/14/2012 through 5/31/2013**
	Approved via Full IRB Review
Principal Investigator:	EDWIN POSADAS
Co-Investigators:	ALAN WAXMAN ROBERT FIGLIN
Other Study Staff:	MIMI LEE KOTY NADEAU NANCY MOLDAWER AMY OPPENHEIM JESSICA HAMANN ZULEMA SANCHEZ THERICA MILLER JENNY JOAQUIN
CSMC Federalwide Assurance No.:	FWA 00000468
Funding Information:	/

Below are the documents currently approved for this study:		
Document Type	**Name**	**Version Description**
Protocol	Protocol Version 5 dated 01Jun11	Protocol Version 5 dated 01Jun11
Investigational Drug Brochure	huJ591 IB IB Stability Addendum	huJ591 IB dated April 14, 2004

INSTITUTIONAL REVIEW BOARD
THE UNIVERSITY OF UTAH
75 South 2000 East Salt Lake City, UT 84112 | 801.581.3655 | IRB@utah.edu

IRB: IRB_00054274

PI: Neeraj Agarwal

Title: Weill Cornell>> A Randomized Phase 2 Trial of 177Lu Radiolabeled MonoclonalCoAntibody HuJ591 (177Lu-J591) and Ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy

This New Study Application has been reviewed and approved by a University of Utah IRB convened board. The convened board approved your study as a Greater Than Minimal risk study on 7/18/2012. The approval is effective as of 7/27/2012 . Federal regulations and University of Utah IRB policy require this research protocol to be re-reviewed and re-approved prior to the expiration date, as determined by the convened board.

Your study will expire on 7/17/2013 .
Any changes to this study must be submitted to the IRB prior to initiation via an amendment form.

DETERMINATIONS

- **Waiver/Alteration Determination:** The IRB has determined that the request for the **waiver of authorization** is approved for this research under 45 CFR 164.512(i).

APPROVED DOCUMENTS

Informed Consent Document
J591 Treatment Consent 07-20-12 Clean.doc

Company Protocol
Lu-J591 Protocol (Version 5 dated 01Jun11).pdf

Investigational Brochure
LuJ591_IB_ver4-14-04 (2).pdf

Recruitment Materials, Advertisements, etc.
Weill Cornell LU Web Posting 2-9-12.doc

Other Documents
J591 Keto pre-screen log.docx
Radiation safety letter.pdf
J591 Medication Diary.pdf
177Lu 1572 Agarwal signed 3-28-12.pdf

U Utah exempt J591 imaging memo 1-9-12.pdf
FDA Sumbission - PI Change to Nanus 9.27.06.pdf
J591 MD Referral Letter 4-27-12.docx
54264 RUS Agarwal signed 2-27-12.pdf
FDA Submission - PI Change to Tagawa 7.16.08.pdf
IND Assignment Letter ORG.pdf

Click IRB_00054274 to view the application and access the approved documents.

Please take a moment to complete our customer service survey. We appreciate your opinions and feedback.

Weill Cornell Medical College

NewYork-Presbyterian Hospital
Weill Cornell Medical Center

Dear Doctor:

You are receiving this letter to inform you of a prostate clinical trial that may be of benefit to your patients. The trial is for men with adenocarcinoma of the prostate previously treated with surgery and/or radiotherapy and now have biochemical progression (rising PSA) after medical or surgical castration. Recruitment is ongoing with additional sites across the country being added.

As you are aware, up to a third of men will develop recurrence of their tumor after local therapy. Some men may be salvaged with radiation after PSA recurrence, but the majority suffer relapse due to microscopic deposits of cancer outside of the radiation field.

In recent years, antibody therapy, or targeted therapy focusing only on cancer cells has shown great promise. J591 is a monoclonal antibody which specifically targets a receptor called prostate-specific membrane antigen (PSMA) located on the surface of virtually all prostate cancer cells. Investigators have developed the ability to attach radioactive isotopes that, when attached to a specific antibody, allow targeting prostate cancer cells, but sparing other or normal cells. Initial trial work (Phase I and II studies in metastatic CRPC) has shown that at the optimal single-infusion dose, 71% of men experienced some decline in PSA after a single injection. Nearly 47% of these men have experienced at least a 30% drop in PSA which is closely associated with a survival benefit in chemotherapy trials.

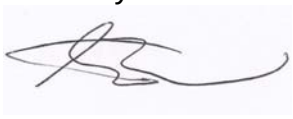
Targeted radiotherapy may be able to overcome the major flaw of salvage radiotherapy: inability to target disease outside of the standard radiation field, when this micro-metastatic disease is not visible using conventional imaging methods. We are currently conducting a multi-center double-blinded Investigator Initiated Phase II trial utilizing a tiny radioactive particle ^{177}Lu linked to one of these antibodies called radiolabeled J591 or ^{177} Lu-J591.

If you have patients who you feel may benefit from participation in this trial and you want to receive more information, provide a referral or participate as an investigative site, please go to http://clinicaltrial.gov/show/NCT00859781. You will find information on sites that are actively recruiting in **New York (NY), Iowa City (IA), Indianapolis (IN) and Los Angeles (CA)** including the primary contact person.

In addition please know that additional investigative sites will be soon open for recruitment in **Atlanta (GA), Salt Lake City (UT), Washington (DC), Pittsburg (PA), New Brunswick (NJ), Kansas City (KC), Houston (TX), St. Louis (MO), Chicago (IL) and Charleston (SC).**

You may also contact me, the Study Chair for the trial Scott Tagawa at Weill Cornell Medical College, stt2007@med.cornell.edu for additional information on the trial and exact information of the locations where you may refer potential subjects.

Sincerely



Scott T. Tagawa, MD, MS